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# What are White Matter Hyperintensities Made of?

## Relevance to Vascular Cognitive Impairment

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**W**hite matter hyperintensities (WMH) of presumed vascular origin, also referred to as leukoaraiosis, are a very common finding on brain magnetic resonance imaging (MRI) or computed tomography (CT) in older subjects and in patients with stroke and dementia. They are associated with cognitive impairment, triple the risk of stroke and double the risk of dementia. Knowledge of their pathology derives mostly from post mortem studies, many from some years ago. These, by their nature, were generally small, sampled from selected brain regions and probably reflect late-stage disease. They focus on features of demyelination and axonal degeneration, which may be easier to detect histopathologically than changes in extracellular fluid. Here we review advances in brain magnetic resonance imaging (MRI) that are revealing white matter hyperintensities at earlier stages, and changes in normal-appearing white matter that indicate tissue pathology, less marked than those found in WMH. These “pre-visible” changes show that altered interstitial fluid mobility and water content, which may be reversible, probably predate demyelination and axonal damage, which are less likely to be reversible and are probably a late-stage phenomenon. Neuroimaging is also revealing the dynamic nature of WMH, their interactions with other pathological features such as secondary cortical and long tract damage, and contribution to accumulating brain damage. These insights provide opportunities to improve understanding the etiology and pathogenesis of small vessel disease, and represents an enormous

unfinished agenda for preventing accumulation of brain damage, and its associated cognitive and physical problems, from mid to later life. Recognizing the earliest stages leading to WMH development will provide important opportunities to prevent (or even reverse) brain damage due to small vessel disease at the earliest stages, and ameliorate its cognitive, physical, stroke and dementia consequences.

## Historical Perspective

Worldwide, about 15 million people have a stroke, from which 6 million die and 5 million are left permanently disabled each year<sup>1</sup>; 35.6 million people worldwide are estimated to be living with dementia, and this is expected to triple by 2050. Although Alzheimer’s disease is the most commonly diagnosed form of cognitive impairment in older people,<sup>2</sup> cognitive impairment due to vascular disease alone, or in addition to Alzheimer’s disease, is very common and contributes to substantial worsening of cognitive function for a given burden of Alzheimer’s disease pathology.<sup>3</sup> The most common form of vascular cognitive impairment typically results in lesions visible on brain scanning known collectively as small vessel disease (SVD) and described in more detail below. Although stroke and dementia are priorities for many governments, the cause of the 20% of strokes and about 40% of dementias attributed to SVD<sup>4</sup> remains unclear, with limited options for prevention and treatment.

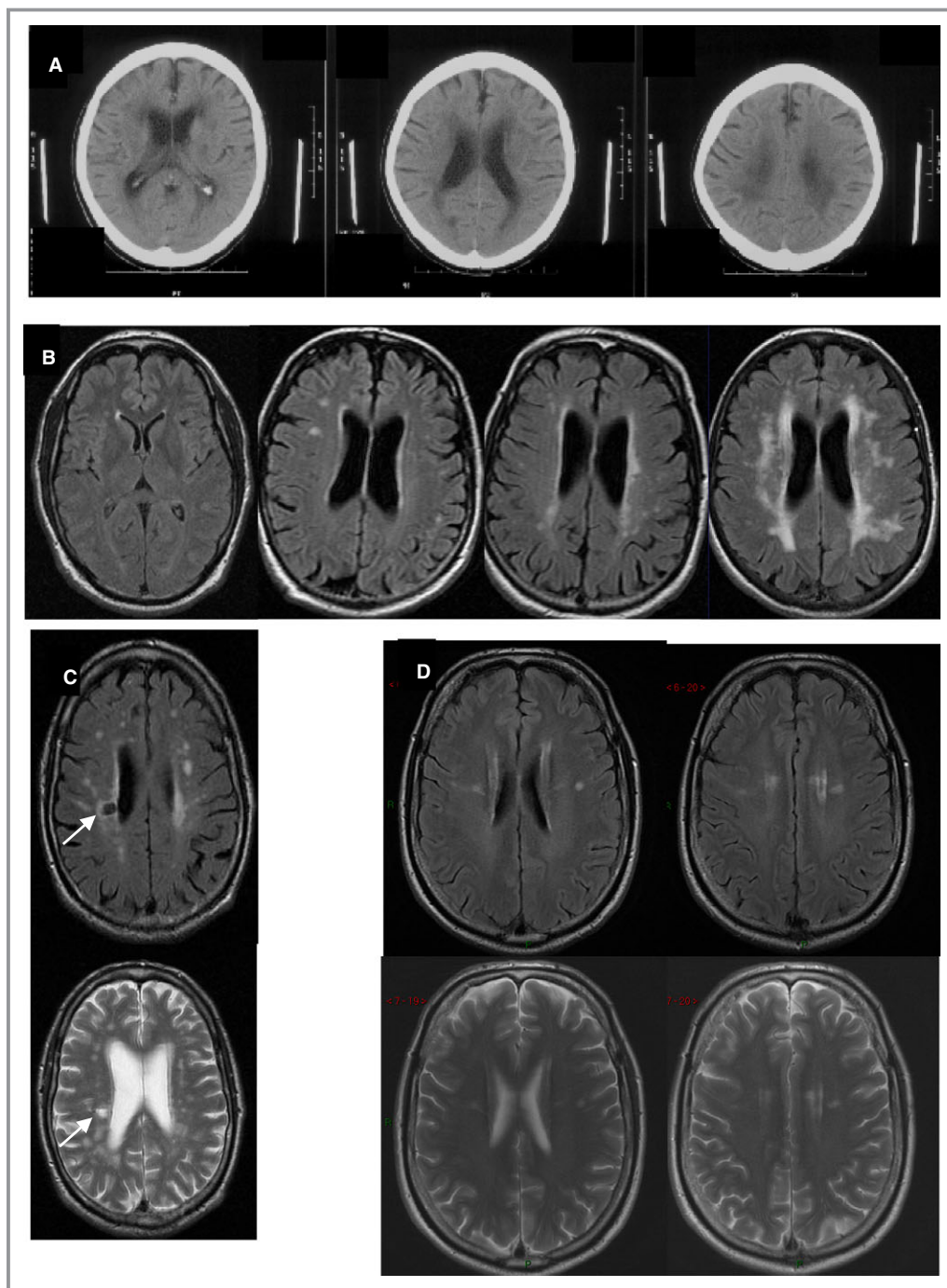
The finding of altered areas of white matter attenuation on computed tomography (CT) was first brought to prominence in the late 1980s by Hachinski and colleagues. They described patchy low attenuation in the periventricular and deep white matter, which they referred to as *leukoaraiosis* (Figure 1).<sup>5</sup> These patchy white matter changes are more obvious as abnormal areas of signal intensity on magnetic resonance imaging (MRI) due to the latter’s better sensitivity to soft tissue changes than CT, particularly for subtle alterations in water content. The signal changes predominate in the periventricular and deep white matter, so were commonly referred to originally as “white matter lesions” although they are also recognized to occur in the deep gray matter.<sup>6</sup> These areas are hyperintense on T2-weighted (T2), proton density-

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**Figure 1.** Examples of WMH on (A) CT, (B) MR FLAIR, (C and D) MR FLAIR and T2-weighted imaging. A, Three adjacent CT images from 1 patient with severe WMH. B, Four different subjects showing, L to R, normal to severe WMH. C, FLAIR and T2-w, same subject, show WMH and a lacune (arrow). D, top FLAIR, bottom T2-w images showing that when subtle, WMH are more easily seen on FLAIR. CT indicates computed tomography; FLAIR, fluid attenuated inversion recovery; MR, magnetic resonance; WMH, white matter hyperintensities.

weighted (PD), and fluid attenuated inversion recovery (FLAIR) MRI sequences, so are now by consensus referred to as “white matter hyperintensities” (WMH), or “subcortical hyperintensities” where deep gray matter is also involved.<sup>6</sup> They are also hypointense on T1-weighted and hyperintense on

T2\*-weighted sequences, but the most sensitive structural sequence for visualizing WMH on MRI is generally the FLAIR sequence (Figure 1).

MRI came into wider use in clinical practice and for research in the late 1980s and early 1990s. Early MRI

scanners of the 1980s–1990s were generally of lower field strength than are available routinely today. This affected their sensitivity. For example, the earliest scanners in clinical use were 0.2 or 0.5 Tesla field strength, and inevitably were less sensitive to subtle tissue changes than are the 1.5 or 3 T MR scanners that are in widespread use today. The early studies also had fewer sequences available and these were less sensitive to brain soft tissue changes than those available now. For example, it was common to use T1-weighted (T1) or T2 sequences, T1 being of similar sensitivity to subcortical changes as is modern CT scanning, while T2 is relatively insensitive to subtle white matter abnormalities and is less good at identifying changes adjacent to a cerebrospinal fluid (CSF)-containing space than is FLAIR (eg, in the immediate periventricular tissues). Hence, when considering imaging-pathological correlations, imaging-clinical, or imaging-cognitive correlations, it is important to bear in mind that early studies of MRI-pathology correlations may have lacked sensitivity to detect the more subtle changes that are visible today, and thus may have influenced our understanding of the pathophysiology towards what are probably more established, permanent changes.

WMH had been overlooked somewhat by pathologists up until CT and MRI became available,<sup>7,8</sup> much of the focus of pathology examinations in the last century being on lacunes (small CSF-containing cavities)<sup>9,10</sup> that are easier to detect pathologically than subtle WMH.<sup>11,12</sup> The diffuse and often subtle changes of WMH may be hard to see macroscopically on brain sections until they are advanced<sup>13</sup>; when subtle, the full extent of WMH may be difficult to appreciate histologically unless specifically sought in aging-related changes<sup>14</sup> or in other white matter diseases such as multiple sclerosis.<sup>15</sup> In contrast, lacunes, ie, small CSF-containing cavities, are more obvious pathologically and had been described in numerous detailed pathology studies (summarized in Bailey et al<sup>16</sup>) although there were not many imaging-pathology correlations for lacunes either.

## Clinical Importance

Until relatively recently, WMH were generally dismissed as inevitable consequences of “normal” advancing age. This is clearly not true. Although WMH do become more common with advancing age,<sup>17</sup> their prevalence is highly variable. Furthermore, numerous studies indicate that they have important clinical and risk factor associations, emphasizing that they should not simply be overlooked as inevitable “silent” consequences of the aging brain.

In a meta-analysis of 22 longitudinal studies, WMH were clearly associated with progressive cognitive impairment, a 2-fold increase in the risk of dementia and a 3-fold increase in risk of stroke.<sup>18</sup> WMH also affect physical function, resulting

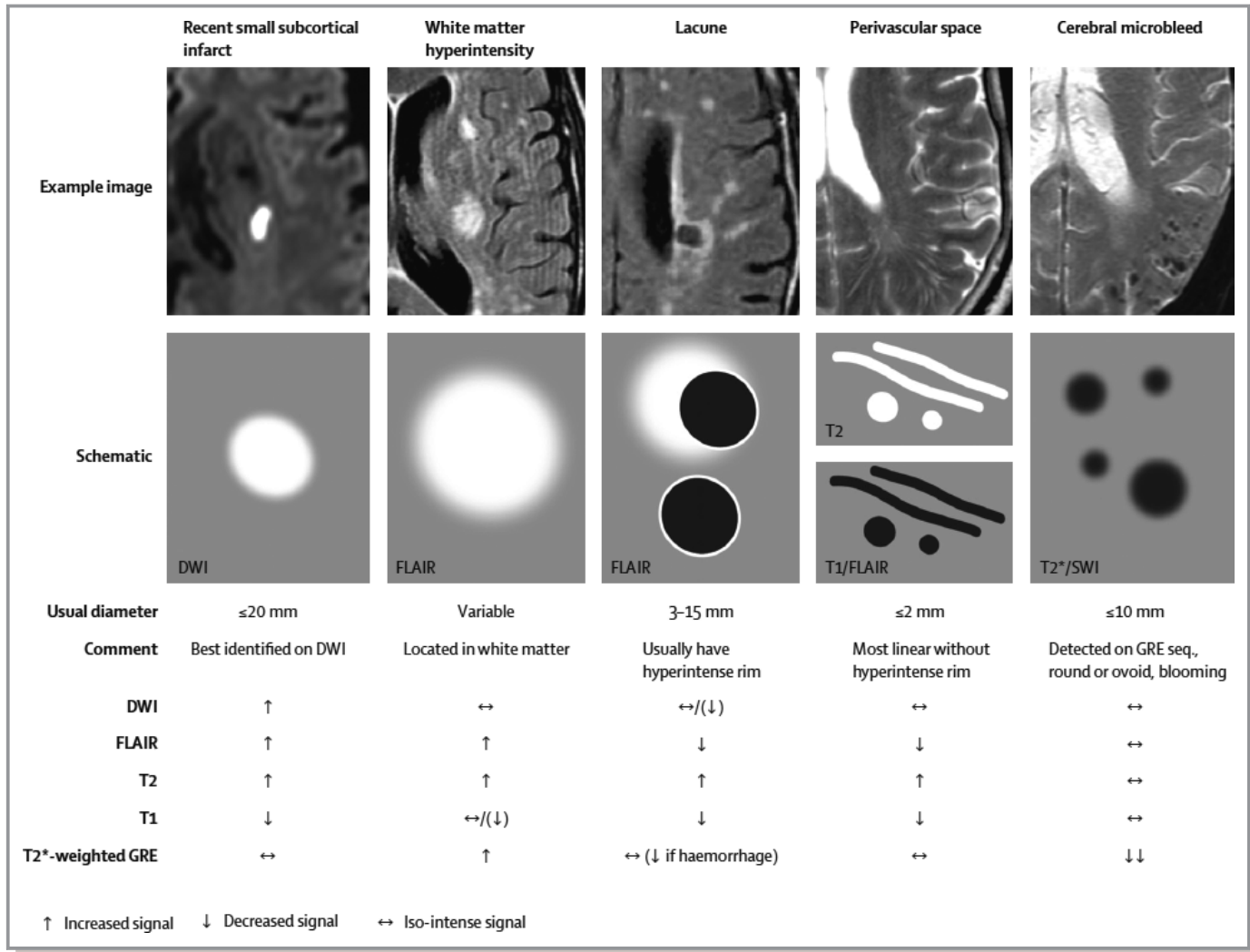
in abnormal gait<sup>19</sup> and disturbed balance.<sup>20</sup> WMH increase the risk of late onset depression.<sup>21</sup> Furthermore, WMH are highly heritable,<sup>22</sup> and they vary with familial longevity being less frequent in subjects with long-lived parents.<sup>23</sup> WMH are inversely associated with intelligence in youth,<sup>24</sup> and with educational attainment.<sup>25</sup> Whether these latter associations indicate relationships between intelligence and risk factor exposure or reflect brain resilience to damage,<sup>26</sup> are as yet unknown.

The prevalence of WMH increases with increasing vascular risk factors, including hypertension,<sup>27–29</sup> diabetes,<sup>30</sup> smoking,<sup>31,32</sup> as well as with many other as yet undetermined risk factors.<sup>33</sup> Risk factor exposure seems to be particularly important if it occurs in middle age,<sup>29,34</sup> but the relative importance of different risk factors may also vary in different age groups. A large multicenter study of WMH in 2699 stroke patients in 11 stroke centers in Korea suggested that raised cholesterol was a more important risk factor for WMH in older hypertensive patients whereas age alone was the major risk factor in older non-hypertensive patients. Diabetes mellitus was an important risk factor in younger non-hypertensives.<sup>35</sup> It is unclear as yet if hypertension has most of its effect directly on the brain, or if it results in systemic vascular stiffening, which in turn affects the brain white matter<sup>36,37</sup> and cognition.<sup>38</sup> Accumulating evidence, including associations with left ventricular hypertrophy, tend to point to the former explanation,<sup>35,37</sup> but more longitudinal studies to determine the sequence of development of WMH in relation to risk factors are required. Additionally, there are as yet mixed results from randomized trials on whether risk factor reduction can prevent WMH progression or cognitive decline in older subjects,<sup>39–41</sup> and some evidence that too aggressive blood pressure reduction in old age could actually worsen white matter damage<sup>42</sup> and cognitive decline, perhaps if autoregulation is impaired through vessel stiffening and loss of vasoreactivity. Further trials of risk factor management are needed and specifically at different ages because different vascular risk factors may have more impact at different ages (eg, hypertension in middle age, cholesterol at older ages<sup>35</sup>). Physical activity is suggested to protect against WMH in cross-sectional studies,<sup>43–45</sup> but whether exercise can prevent progression or development of WMH remains to be tested in randomized clinical trials.

WMH are part of the spectrum of small vessel disease (SVD) which includes lacunar (or small subcortical) ischemic and hemorrhagic stroke, lacunes, microbleeds, perivascular spaces and brain atrophy (Figure 2).<sup>6,46</sup> All of these features, individually, are associated with cognitive impairment,<sup>47–51</sup> even when subtle.

The dynamic nature of these inter-related lesions is illustrated by studying patterns of lesion evolution (Figure 3): acute small subcortical infarcts can disappear (10%), remain looking like a WMH (60% to 70%), or cavitate to form a lacune





**Figure 2.** STRIVE examples of different features of small vessel disease, including white matter hyperintensities. Reproduced with permission from Wardlaw et al.<sup>6</sup> DWI indicates diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; GRE, gradient recalled echo; STRIVE, standards for reporting vascular changes on neuroimaging; SWI, susceptibility-weighted imaging.

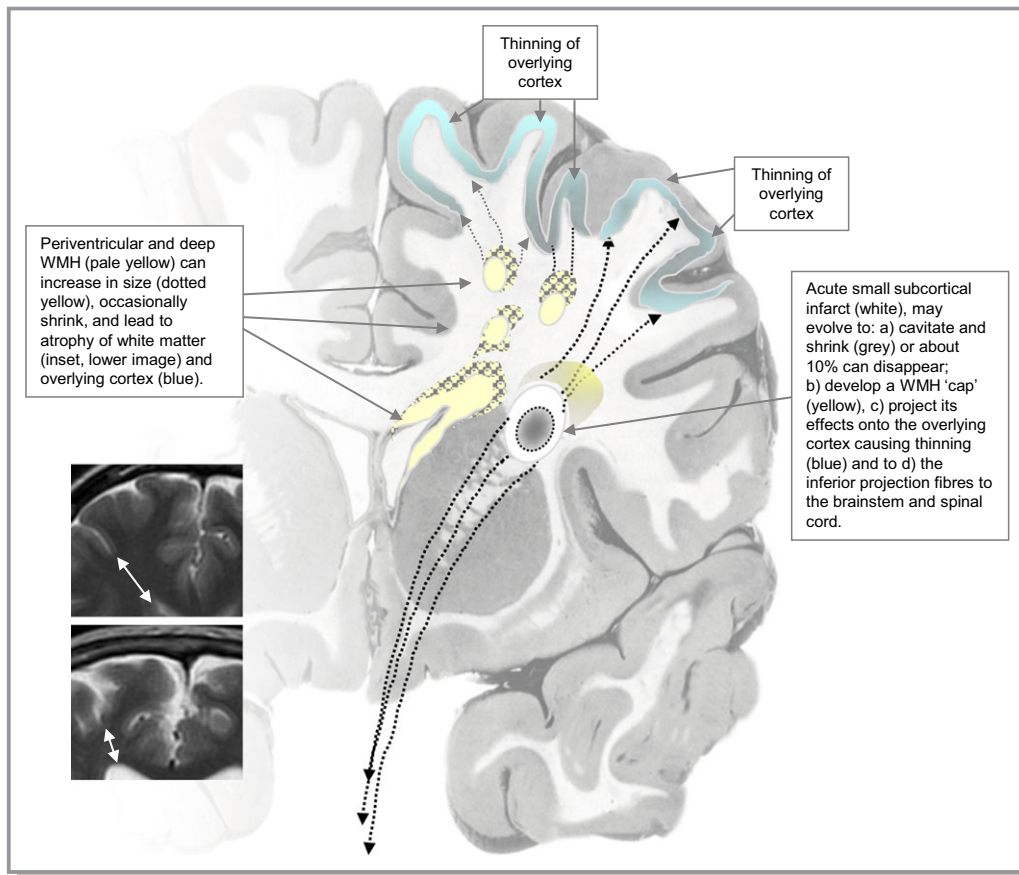
(20% to 30%)<sup>52–54</sup>; lacunes may form at the edge<sup>55</sup> or (in our experience) in the middle of a WMH; WMH can “grow” at the edges of small subcortical infarcts<sup>56</sup>; incident lacunes<sup>57</sup> and WMH<sup>58</sup> are associated with cortical thinning and cerebral atrophy<sup>59</sup>; all of which indicate progressive and accumulating brain damage. Furthermore, WMH increase risk of brain damage in the presence of other pathologies, for example, they associate with infarct growth and worse outcome after large artery stroke,<sup>60,61</sup> and they predict poor functional stroke outcome.<sup>62–64</sup>

The effects of all these SVD features on cognition are cumulative,<sup>65</sup> (in submission) providing further indication that together these SVD features are closely related pathologically,<sup>52</sup> and represent cumulative brain damage,<sup>32</sup> the prevention of which should help ameliorate brain tissue damage, reduce loss of normal brain cognitive and physical function and preserve independent survival in old age.<sup>43</sup>

### What Do Pathology Studies Suggest That WMH Are Due To?

Pathology studies are, unfortunately, infrequent<sup>12,66,67</sup> compared with the number of WMH captured in imaging studies. There are particularly few pathology studies that have linked individual lesions seen on MRI with their pathological examination.<sup>12,68,69</sup> Pathology studies have been hampered by difficulty in matching up individual small lesions on imaging with their pathological counterpart,<sup>11,68</sup> with limitations of sampling,<sup>13</sup> of fixation,<sup>70</sup> of definitions,<sup>71–73</sup> they provide “snapshots” of disease evolution, and because end-stage damage may obliterate the earliest stages of disease.

As described above, the earlier pathology reports focused on demyelination and axonal loss in WMH<sup>7</sup> and described the changes as “ischemic”.<sup>74,75</sup> Demyelination and axonal destruction imply that the changes are permanent. Indeed,



**Figure 3.** Diagram of dynamic mechanisms by which WMH and SVD lead to brain damage. SVD indicates small vessel disease; WMH, white matter hyperintensities.

extensive WMH were associated with reduced density of glia and vacuolation.<sup>8</sup> More subtle WMH on MRI were associated with microglial and endothelial activation.<sup>13</sup> Some studies differentiate periventricular from deep WMH<sup>12,76,77</sup> although imaging studies indicate that periventricular and deep WMH are probably mostly part of a continuous pathology.<sup>76,78</sup> A recent very large study in 2699 patients with stroke from 11 stroke centers in Korea created statistical maps of WMH distribution and provided more evidence to support treating periventricular and deep WMH as a continuous pathology, any apparent difference in distribution in some patients simply reflecting an earlier stage in disease.<sup>35</sup> Notwithstanding, the available pathology describes periventricular WMH as having discontinuous ependyma, gliosis, loosening of the white matter fibers, and myelin loss around tortuous venules in perivascular spaces,<sup>11,12,79</sup> the gliosis, demyelination, and fiber loss worsening as the periventricular WMH worsened. In deep WMH, there was demyelination, gliosis, and axonal loss around perivascular spaces, with vacuolation and increased tissue loss as the lesions became more severe.<sup>12</sup> The changes were heterogeneous.<sup>77</sup> WMH in patients with AD showed more microglial activation than in WMH of age-matched controls.<sup>80</sup> The variation in pathological severity might help explain some

of the variation in the association between WMH severity and cognitive change in old age<sup>80</sup> although this needs to be verified in larger and more heterogeneous populations with good cognitive, dementia and SVD phenotyping.

Some reports indicate the presence of proteins in the perivascular tissues in human WMH<sup>81</sup> and suggest that the arteriolar wall thickening seen in SVD is also a consequence of the movement of plasma proteins into the vessel walls.<sup>82</sup> The proteins include fibrinogen, immunoglobulins, thrombomodulin,<sup>83</sup> and occur in subcortical grey and white matter and are also seen in normal appearing white matter and are associated with microglia.<sup>81</sup> The microglia and proteins were more frequent in areas of WMH with more advanced tissue loss.<sup>81</sup> Increased albumin was found in the interstitial tissues of brains of older subjects with WMH<sup>84</sup> although it was uncertain as to where the albumin had come from in this study as the endothelial tight junction proteins were said to be intact. Others have not identified direct evidence of blood-brain barrier (BBB) impairment despite identifying proteins associated with endothelial activation<sup>83</sup> and that had extravasated into the perivascular tissues.<sup>85</sup> However, the cerebral blood flow and the cerebrovascular endothelial surface area are both so large that there would not have to be much

breach of the BBB for proteins and fluid to accumulate in the interstitial spaces. It is likely also that such tissue fluid shifts are difficult to identify pathologically or overlooked as fixation artifact, where fixation methods involve freezing or dehydration, which may affect tissue content.<sup>70</sup>

Numerous *in vivo* studies have found raised CSF:plasma albumin ratios with advancing age, in patients with Alzheimer's disease, in vascular dementia, and in patients with WMH,<sup>86</sup> and suggested a role for chronic brain edema in forming WMH and more advanced damage in the form of lacunes.<sup>87–89</sup> Undoubtedly the pathological picture is mixed and complex<sup>90</sup>: despite the risk factor association, immuno-histochemical and gene expression microarray studies suggesting a role for ischemia, hypoxia, or hypoperfusion, studies also show immune activation, BBB dysfunction, altered cell metabolic pathways, and glial injury.<sup>90</sup> The abnormalities are now being recognized in normal-appearing white matter as well as in WMH. Therefore, regardless of where the albumin or other plasma proteins came from, or how they got into the interstitial tissues, there does appear to be a role for loss of normal BBB function and fluid shifts into the brain leading to secondary brain damage<sup>91,92</sup>; if arrested or reversed early, the interstitial fluid shifts may be more reversible than demyelination and axonal loss.

## What Does Imaging Suggest?

To understand more about the pathophysiology of WMH, we must turn to imaging methods that allow us to detect and quantify subvisible tissue changes on a per voxel basis *in vivo*. Structural changes in the integrity of the brain's white matter are commonly observed through MRI methods such as diffusion tensor imaging (DTI), a widely available imaging technique that provides quantitative measures of the mobility of water molecules *in vivo*. Parameters obtained from the water diffusion tensor are used as diagnostic markers for clinical applications. The most commonly used are fractional anisotropy (FA), which indicates the deviation from pure isotropic diffusion of water mobility *in vivo*, and mean diffusivity (MD), which measures the magnitude of diffusion of the water molecules.<sup>93</sup> Both the magnitude and directionality of the water diffusion are affected by the underlying tissue architecture and can demonstrate, for example, alterations in axonal microstructure or interstitial fluid.<sup>94–98</sup>

Further potential MRI biomarkers of white matter damage are the magnetization transfer ratio (MTR) and the longitudinal relaxation time (T1). MTR is obtained from magnetization transfer MRI<sup>99</sup> and can show pathological changes in the white matter structure that involve macromolecules in the cell membrane, such as inflammation or demyelination.<sup>100</sup> T1 relaxation time is a weighted average of the free and bound water phases<sup>101</sup> providing quantitative information on brain

water content, and is therefore a potential marker for edematous brain tissue.<sup>94</sup>

Other methods of assessing alterations in normal brain tissue function use dynamic imaging following intravenous injection of a contrast agent. In dynamic contrast-enhanced MRI<sup>102</sup> a series of T1-weighted images are acquired dynamically after injection, enabling the measurement of BBB permeability.<sup>103,104</sup> Similarly, dynamic susceptibility contrast MRI is used to measure cerebral perfusion and estimate regional cerebral blood volume and cerebral blood flow (CBF), again by tracking a contrast agent bolus using a T<sub>2</sub>\*-weighted sequence.<sup>105,106</sup>

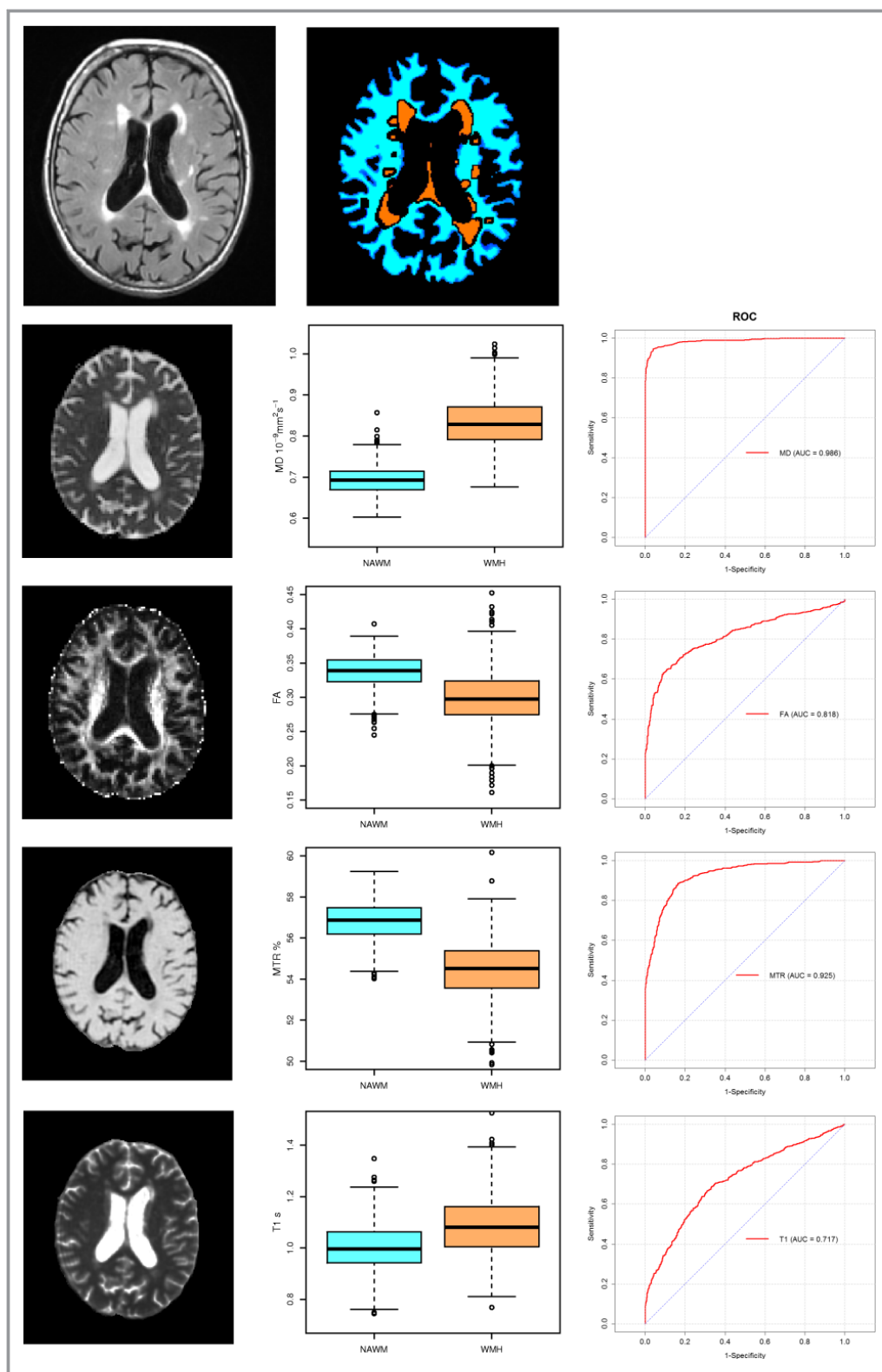
The measurement of these MR imaging biomarkers in addition to structural “visible” brain changes, can help to identify the pathophysiological changes within normal-appearing white matter and WMH *in vivo* and inform our understanding of their pathophysiology.

Studies in humans have shown that MD and T1 increase while FA and MTR decrease significantly in areas of WMH when compared to normal appearing white matter,<sup>98,107–109</sup> indicating pathological processes involving increased water content and mobility, demyelination, and axonal loss. MD was reported as the parameter that discriminated best between normal-appearing white matter and WMH (Figure 4).<sup>109</sup> Perfusion MRI studies also showed decreased CBF in regions of WMH,<sup>110,111</sup> although it remains uncertain as to how much the blood flow reduction represents reduced flow due to having less tissue to supply but is not the primary cause of the damage,<sup>37,112</sup> or is the primary cause of worsening of tissue damage.<sup>113,114</sup> there is some evidence for both explanations.<sup>115</sup> The dynamics of WMH progression and associations with CBF are complex and regionally specific.<sup>116</sup>

Imaging demonstrates that WMH are heterogeneous, ie, they represent different amounts of tissue damage, as reflected in their degree of “whiteness” and in features seen on more recent MR scanners such as “dirty white matter” (Figure 5). Moreover, studies using MTR show that MTR differs between frontal and occipital WMH,<sup>117</sup> either indicating different stages of tissue damage or possibly different underlying tissue constructs.

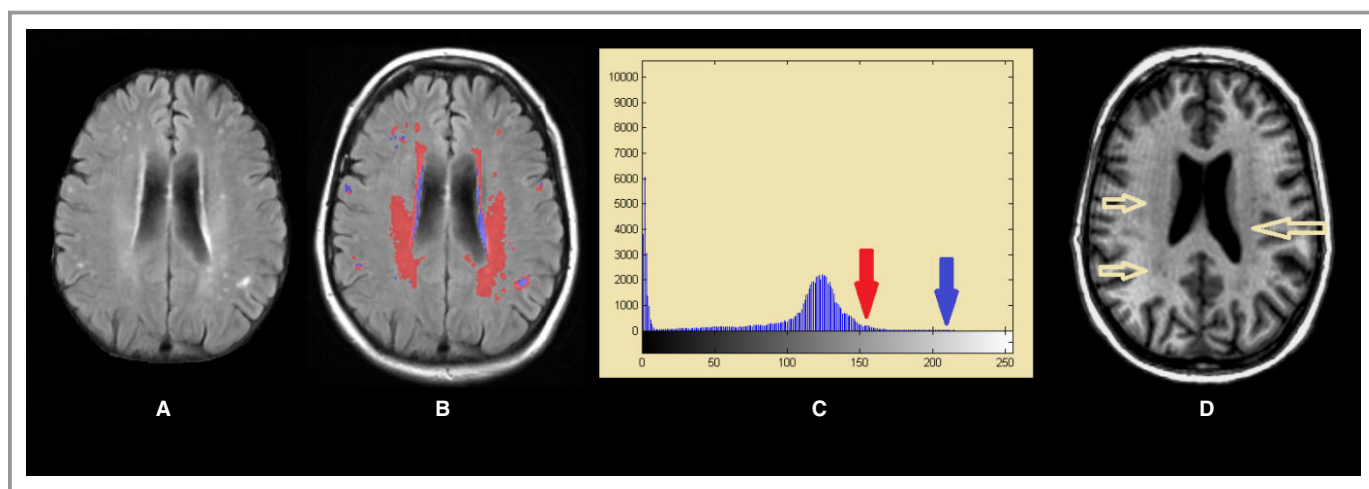
The relationships between different parameters observed in WMH differed from those relationships in normal-appearing white matter (Figure 6). Significant correlations appeared between MTR and both FA and MD in WMH, whereas these parameters were not correlated in normal-appearing white matter, indicating that cellular breakdown in WMH allows quantitative MRI parameters to take a much wider range of values than in healthy tissue, where they are kept within tight bounds and are likely to be independent.<sup>98</sup>

Several reports indicate that the tissue structural and vascular changes spread further than the visible area of the WMH, rather than being confined to the visible WMH<sup>109,111,118–120</sup>



**Figure 4.** Images for FA, MD, T1, and MTR and corresponding values in normal-appearing white matter and WMH. And corresponding ROC curves for each parameter's ability to differentiate normal white matter from WMH. MD shows a near perfect ROC curve. Top 2 images show the original FLAIR image and the tissue segmentation into normal white matter and WMH. FA indicates fractional anisotropy; FLAIR, fluid attenuated inversion recovery; MD, mean diffusivity; MTR, magnetisation transfer ratio; NAWM, normal-appearing white matter; ROC, receiver operator characteristic; WMH, white matter hyperintensities.



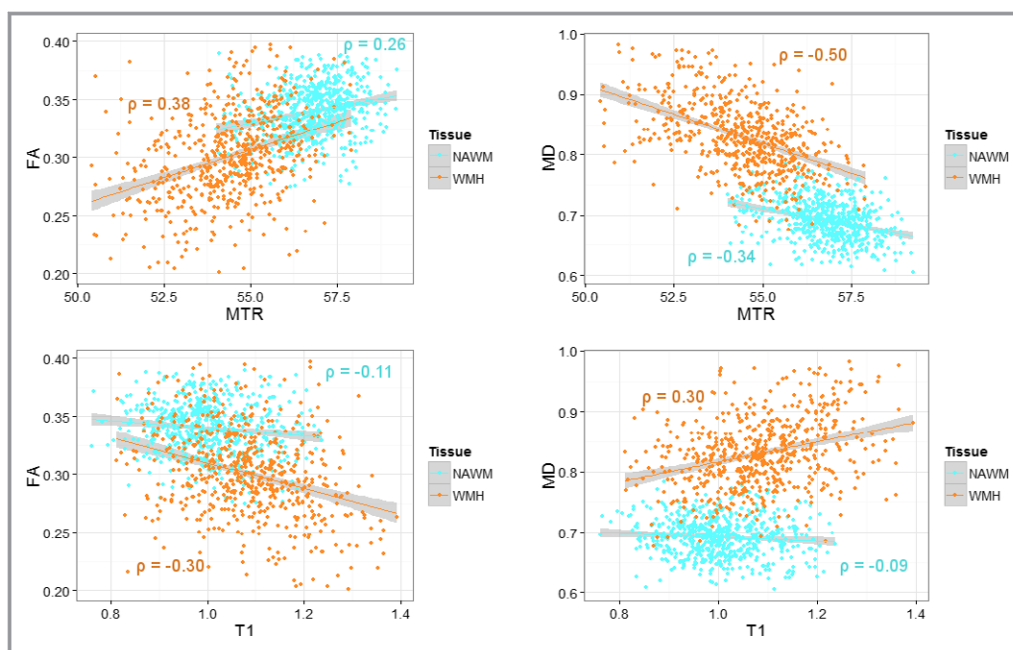


**Figure 5.** FLAIR image through the lateral ventricles showing severe (ie, intense) WMH and less-intense white matter damage (A), represented in blue and red, respectively in (B) and which correspond with the intensities arrowed in the histogram (C). Less-intense damage can be also observed in the T1-weighted modality as the yellow arrows show (D). FLAIR indicates fluid-attenuation inversion recovery; WMH, white matter hyperintensities.

consistent with recent pathological reports.<sup>90</sup> The changes radiate into normal-appearing white matter, particularly in the immediate peri-WMH tissue, indicating that the underlying pathology is a diffuse process affecting much of the white matter and even other parts of the brain, and that visible lesions, ie, the WMH, are probably only the “tip of the iceberg.”

This compromised normal-appearing white matter integrity in the presence of WMH has been observed through different

quantitative imaging techniques. For example, CBF<sup>121</sup> and cerebrovascular reactivity were reduced and BBB permeability was increased in the normal appearing white matter of healthy elderly subjects and all were associated with the presence of WMH.<sup>122</sup> BBB permeability increases with advancing age during normal aging, but is further increased in dementia particularly in patients with vascular dementia and in patients with WMH.<sup>86</sup> Others have found increases in



**Figure 6.** Correlations between FA, MTR, MD and T1 in NAWM and WMH. In general, the T1 and FA, MD and MTR show stronger correlations in WMH than in NAWM. FA indicates fractional anisotropy; MD, mean diffusivity; MTR, magnetization transfer ratio; NAWM, normal-appearing white matter; WMH, white matter hyperintensities.

BBB permeability in NAWM in patients with WMH,<sup>123</sup> in patients with lacunar versus cortical ischemic stroke, with increasing age and numbers of enlarged perivascular spaces,<sup>124</sup> and in WMH in vascular dementia.<sup>125</sup> The MD and FA of NAWM have been also associated with WMH volume.<sup>120,126–128</sup>

However, studies typically include subjects of widely varying age and the changes observed in NAWM integrity relative to WMH load could also be a consequence of the older age of those subjects with more WMH.<sup>17,129,130</sup> A more recent study in a large cohort of older people of near-homogeneous age reported that FA, MD, MTR, and T1 were all associated with the severity of WMH (highest Fazekas scores) – even after accounting for age, gender, exposure to common vascular risk factors and the proximity to WMH – proving that the changes observed were not just a function of age.<sup>109</sup> Moreover, although all 4 parameters measured in NAWM were related to WMH severity in those with most WMH, only the MD of NAWM showed changes within the mildest range of WMH. Additionally, of the 4 quantitative parameters of MD, FA, MTR and T1, it was MD that showed the best differentiation of WMH from normal-appearing white matter, performing substantially better on receiver operator characteristic (ROC) curves than did FA, MTR, or T1. This combination of findings suggests that the earliest pathological processes responsible for WMH involve changes in interstitial fluid mobility.<sup>109</sup>

Although observed by others,<sup>98</sup> the concept of “WMH penumbra” was introduced by Maillard et al<sup>118</sup> after they observed that the effects on FA are not only globally influenced by the WMH load, but also locally influenced by the distance into normal-appearing white matter from the edge of the WMH. This idea of the more abnormal the tissue, the closer the proximity to the WMH, was recently corroborated by measuring MRI quantitative parameters in the normal-appearing white matter in “contours” set at increasing distance from the visible edge of the WMH on FLAIR. In this contour-based analysis, MD decreased and MTR increased with increasing distance from the WMH over all distances assessed, whereas FA and T1 mainly showed only slight changes in the closest contours to the WMH (Figure 7).<sup>109</sup>

Longitudinal studies suggest that people with lower white matter integrity at baseline are more likely to progress to cognitive impairment or frank Alzheimer’s disease than are those with higher white matter integrity.<sup>131</sup> Having a high WMH burden increases the risk of worsening WMH several years later,<sup>132</sup> as well as of stroke, dementia, and death.<sup>18</sup> New lacunes form at the edges of WMH<sup>55</sup> and WMH form at the edges of small subcortical infarcts or lacunes,<sup>56</sup> ie, damage begets damage (Figure 3).

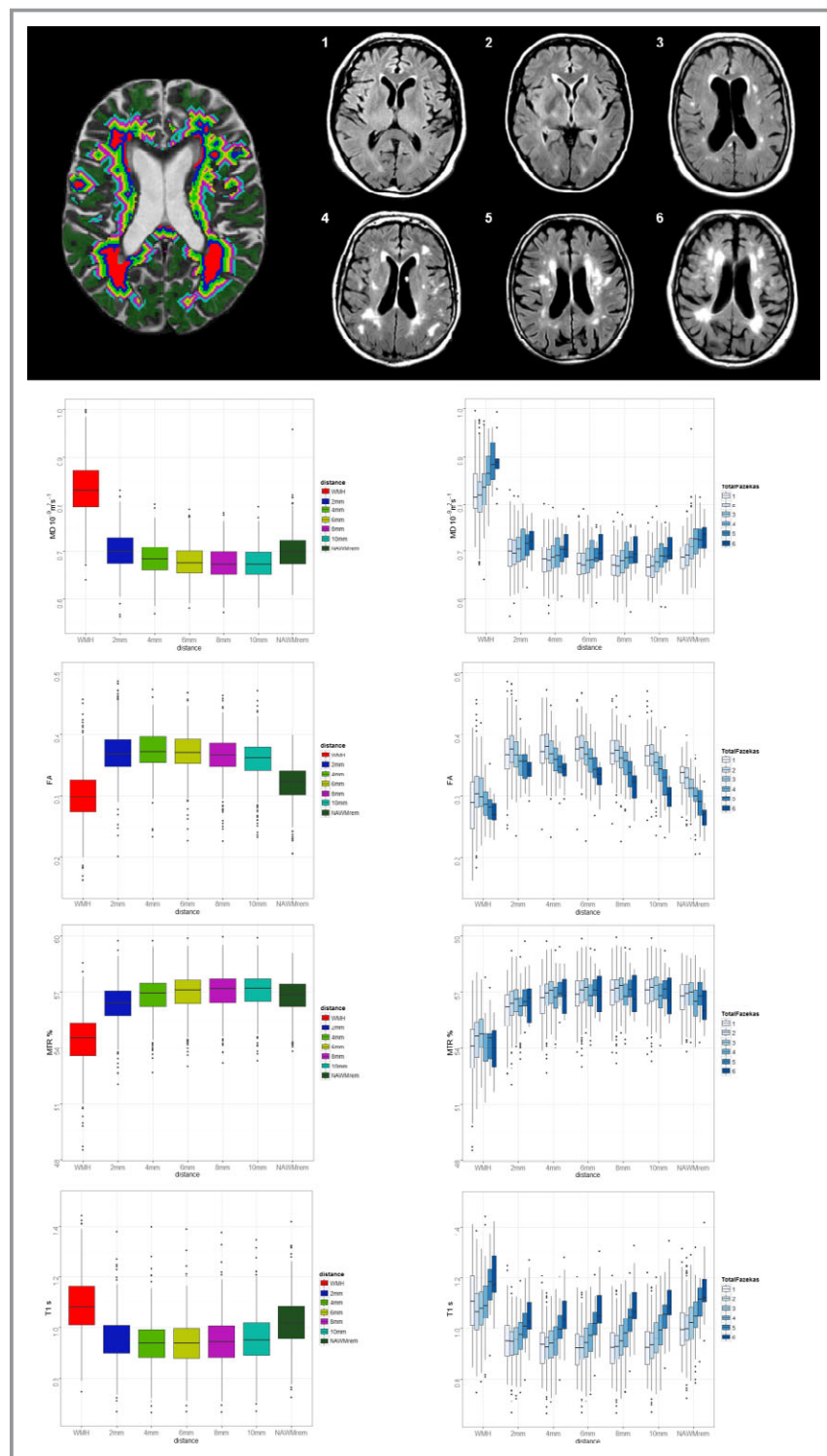
The precise sequence of pathologic processes underpinning the microstructural changes in white matter integrity within and around WMH are yet to be fully described.

Pathology studies have described rarefaction, demyelination, and axonal loss in WMH as outlined above, which are compatible with the observed increases in MD and T1, and the decreases in FA, MTR, and CBF detected using neuroimaging. Some changes such as minor fluxes in fluid content may be relatively easier to detect with MR imaging, which is highly sensitive to water shifts. Hence, neuroimaging *in vivo* is highly complementary to pathology by providing tools to aid the identification of the earliest stages in the pathological processes that end in the development of visible WMH.<sup>46</sup> The increase in MD in NAWM seen even in the presence of the mildest WMH burden, and the fact that this parameter also provides excellent discrimination between both tissue types on ROC curves, suggests that altered mobility of interstitial fluid occurs earlier in the developing pathology of WMH in the aging brain than do changes in myelin (MTR), axonal integrity (FA), or total water content (T1). However, further work relating these imaging biomarkers to histopathological findings, especially at early stages in disease, and in longitudinal studies, is required to understand fully the pathological processes that are responsible for white matter damage within and around the WMH.

## Limitations of Imaging Approaches to Determining WMH Pathophysiology

MRI processing methods for WMH detection and differentiation from artifacts, co-registration of different types of images, and image processing methods such as bias field correction, affect measurements of lesions and brain tissue parameters. The full analysis of these limitations is beyond the remit of this paper, but these limitations are important but rarely mentioned in imaging papers so are discussed briefly here for completeness. Indeed the full scope of the effects of these limitations is only just beginning to be understood by the clinical research community.

Methods to quantify WMH volume are evolving rapidly. Many were developed for use in one study, reflect the particular subject, image acquisition characteristics and WMH burden of that study population. Few, if any, are in use in clinical practice. Many research groups develop their scanning protocol and WMH segmentation approach and apply it to subsequent studies, without further validation. The protocol may not be changed or improved partly due to lack of availability of source codes and/or software and because of a natural desire to minimize the effect of protocol changes on measured variables. Most studies use a semi-automatic thresholding approach to identify WMH on FLAIR images. These threshold selection methods may then be applied in different studies assuming that the reliability will not change, which is unlikely to be correct as FLAIR images are not quantitative and the signal to noise ratio may not be the



**Figure 7.** Effect on MD, FA, MTR, and T1 of increasing burden of WMH, in the WMH and at 2 mm distance increments from the WMH edge into the NAWM (2 mm-NAWMrem). Top left, illustrates WMH (red) and contours (different color bands), right, 1 to 6, WMH Fazekas scores. Lower left graphs show change in the 4 MR parameters from WMH and at increasing distance into the NAWM; lower right graphs show the parameter changes at increasing distance into NAWM split by total WMH burden (Fazekas score). Adapted from Muñoz-Maniega et al.<sup>109</sup> FA indicates fractional anisotropy; MD, mean diffusivity; MTR, magnetisation transfer ratio; NAWM, normal-appearing white matter; WMH, white matter hyperintensities.

same. Thresholding on a single image such as FLAIR requires individualized thresholds (“one size” does not “fit all cases”); multispectral approaches using several sequences combined are more accurate.<sup>133</sup> A full description of the WMH volume measurement methods used in different studies to date is beyond the scope of this paper but is available upon request.

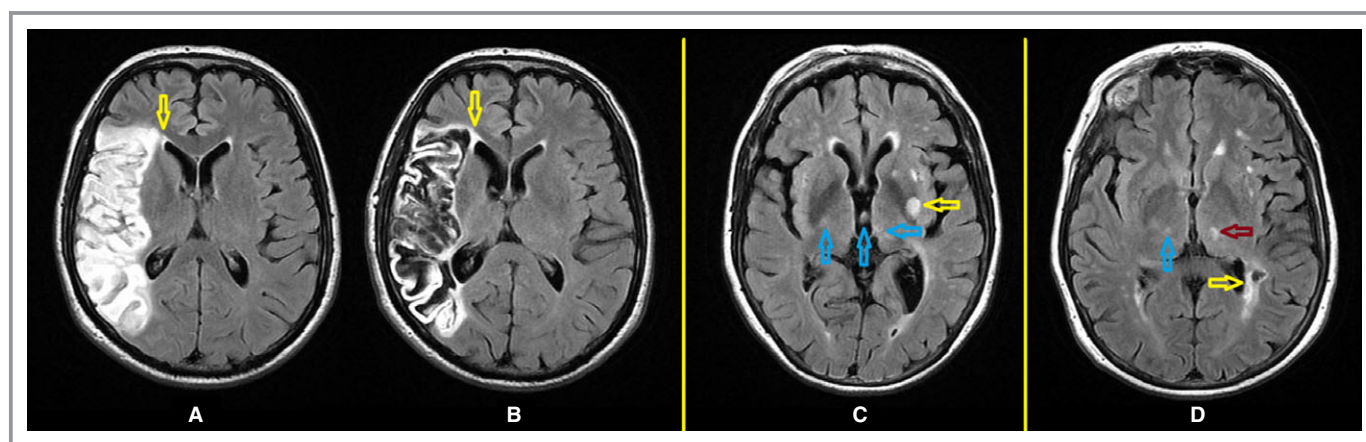
WMH volume measurement is time consuming, hence larger studies seek automated approaches but it is not known whether all studies check each case individually for the accuracy of segmentation, or the rigor with which this is performed where done. However, there is as yet no automated approach that can identify WMH accurately without any human input – all require visual assessment and manual correction, particularly in populations with advanced age or stroke where the brains are more likely to be abnormal (Figure 8) and features of similar signal characteristics like stroke lesions, if not excluded, will distort the WMH volume measurements with subsequent alterations on the outcome of the study.<sup>134</sup>

Artifacts that mimic WMH (to a computer algorithm) are numerous (Table) and require manual editing.<sup>135,136</sup> Guidelines exist to differentiate WMH from artifacts,<sup>135,137</sup> but these lack uniformity and consensus. Some class periventricular hyperintense thin lines around the lateral ventricles as artifact,<sup>135,139</sup> but others found a high correlation between signal intensity levels and width of the periventricular WMH, total WMH volumes, periventricular WMH severity, vascular risk factors, and stroke,<sup>76</sup> indicating that periventricular WMH are true tissue abnormalities and should not be considered artifacts.<sup>78</sup>

Differentiating WMH from other SVD lesions such as perivascular spaces<sup>6,8,150</sup> and lacunes<sup>6</sup> may be difficult. Differences in magnet strengths can lead to inconsistent

assessment of WMH, eg, subtle tissue changes in normal-appearing white matter could go unnoticed at 3 T due to noise<sup>151,152</sup> or vice versa (Figure 9).<sup>153</sup> Reported mean intra- and inter-scanner coefficients of variation in automatic volumetric measurements of brain structures range from 0.87% to 15.1% (median 4.80%). Only limited information is available for the range of values for direct comparisons of WMH assessed at 1.5 and 3 T.<sup>153,154</sup>

Image registration methods impose limitations, eg, native versus standard space, atlases, and registering structural to DTI or other echoplanar images, all can distort lesion location and size. In one study of recent small subcortical infarcts of <1.5 cm diameter, we found that the volume of some acute lesions was more than doubled if measured after registering the image in standard space against a routinely available atlas, rather than performing the measurement in native space (ie, on the patient's own brain scan) prior to registration. Mapping the images of interest against brain atlases allows analysis of lesion distribution (eg, lobar distribution, vascular territories, etc), but relies on accurate registration of a brain template to the brains of the subjects in the population of interest. While state-of-art non-linear registration methods<sup>155</sup> have demonstrated very good performance, these have yet to be tested in SVD or aging studies. This is important as it may influence perceived lesion or tract location and represents a complex challenge that needs to be addressed. In general, atlases should be used that are as representative as possible of the age range and population of interest. Unfortunately, no atlases as yet include structures that are typically affected by WMH, such as the major arterial “borderzones,”<sup>156</sup> but variation in vascular territories may account for some variation in WMH burden.<sup>157</sup>



**Figure 8.** Some factors which confound the delineation of WMH. FLAIR axial images from a patient 4 days after a stroke (A) and a year later (B): while the boundary of the periventricular WMH can be well perceived on the baseline scan, it coalesces with the large infarct after a year (yellow arrow) making it impossible to quantitatively determine accurately the increase in the stroke lesion separated from the increase in the WMH. Different patient (C) has a recent small subcortical stroke lesion arrowed in yellow, and artifacts arrowed in blue; (D) a lacune (yellow arrow) confluent with the periventricular WMH, real thalamic hyperintensity arrowed in magenta and thalamic artifact arrowed in blue create difficulties for measuring the WMH. FLAIR indicates fluid attenuation inversion recovery; WMH, white matter hyperintensities.



**Table.** Common Artifacts That Confound the Identification of WMH on FLAIR MRI

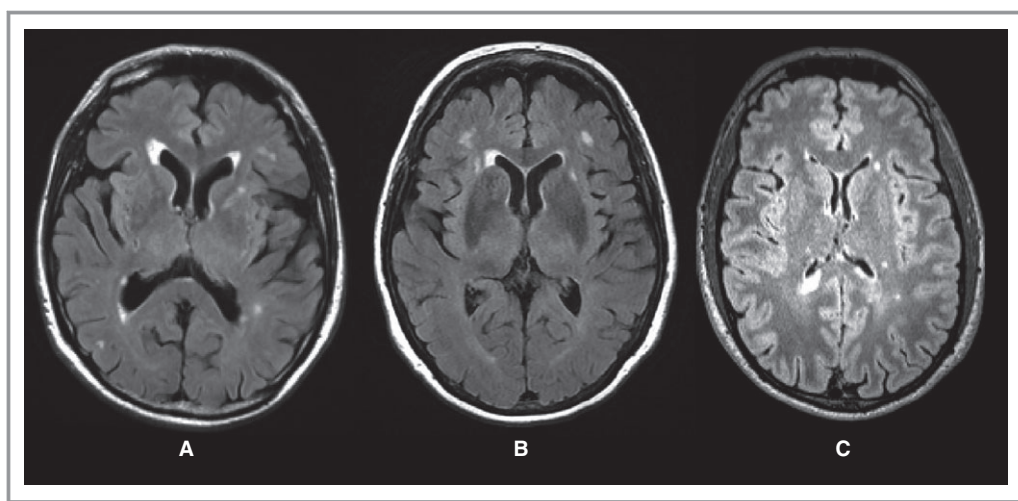
| Artifact Type                              | Artifact Location  | Characteristic Effect   | References            |
|--|--|---|-----------------------|
| CSF flow                                   | Fourth ventricle, aqueduct, cistern ventral to mesencephalon | Hyperintense tissue surrounding these structures; periventricular hyperintensity with constant gradient   | 136,138–145           |
| CSF flow                                   | Bilateral sylvian fissures and insular cortex                | Uniform hyperintensity along the external capsule   | 136,146,147           |
| CSF flow                                   | Third ventricle and Fornix                                   | Hyperintense tissue surrounding the third ventricle and fornix; diffuse periventricular hyperintensity gradually decreasing in strength towards the antero-medial thalamic nucleus and internal capsule | 136,140,142,144,147   |
| CSF flow                                   | Lateral ventricles   | Hyperintense cluster near the walls of the anterior horns of the lateral ventricles   | 136, 140,142, 144,147 |
| CSF flow                                   | Choroid plexus   | Small hyperintense cluster above the temporal horns of the lateral ventricles   | 144                   |
| Corticospinal tract                        | Pathways of the corticospinal tracts                         | Bilateral and symmetric hyperintensities with similar signal level in the junction between the internal capsule and the medial thalamic nucleus   | 147                   |
| Magnetic field susceptibility              | Amygdaloid nucleus and anterior temporal poles               | Wide hyperintense clusters covering the amygdaloid nucleus and the anterior temporal poles  | 136,145,148           |
| Magnetic field susceptibility and CSF flow | Cingulate gyrus  | Hyperintense tissue along the longitudinal cerebral fissure on the anterior section and on the territory of the anterior cerebral artery  | 136                   |
| Patient motion (eye movement)              | Around the eyes  | Ghosting effect on tissue around the eyes   | 136,143               |
| Patient motion (Head movement)             | Throughout the whole image                                   | Concentric hyperintense rings that distort/mask real WMH  | 136,138,148,149       |
| Image reconstruction (Gibbs ringing)       | Throughout the brain accentuated near the skull borders      | Concentric hyperintense rings that follow signal intensity borders and distort/mask small WMH   | 145                   |
| Blood flow                                 | Near the sinuses and main arteries                           | Small linear hyperintensities near the sinuses and carotid arteries   | 145                   |

Note, only publications that were dedicated to analyse and describe these artifacts on FLAIR MRI and/or propose methods to compensate them are referenced. CSF indicates cerebrospinal fluid; FLAIR, Fluid Attenuated Inversion Recovery; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

Irrespective of the method used to quantify WMH, one factor that affects the assessment of WMH is the subtle variation in the radio-frequency magnetic field known as magnetic field inhomogeneity. Image processing methods that correct for magnetic field inhomogeneities have been used in some studies.<sup>158–162</sup> Some of these methods are scanner and protocol-specific<sup>159,162</sup> while others are part of publicly available software where the algorithms assume that the software is applied to brain images with only voxels containing CSF, gray matter, and white matter, after all other tissue types are removed (<http://brainsuite.org/processing/surfaceextraction/bfc/>, <http://bioimagesuite.yale.edu/manual/guide/correction.aspx>). If applied to FLAIR images with WMH, these tools may try to remove the WMH or focal infarcts, which are interpreted as inhomogeneities (Figure 10). Hence, these methods should be avoided until it is clear that they do not simply remove the WMH or alter their apparent distribution.

Two final features of WMH that have been overlooked to date are (1) the presence of ill-defined subtle hyperintense white matter that are non-continuous and diffuse, with varying erratic intensity patterns emerging from the lateral ventricle walls, sometimes known as “dirty white matter”<sup>163</sup> and which may be an indicator of pre-lesional changes (Figure 5); and (2) the fact that WMH can get smaller or disappear rather than continuously enlarging (Figure 11). “Dirty white matter” is probably a real feature indicating subtle tissue damage, as suggested by the signal change in Figure 5. It will influence where the boundary of the WMH is set and hence associations with other MR parameters like FA and MD.

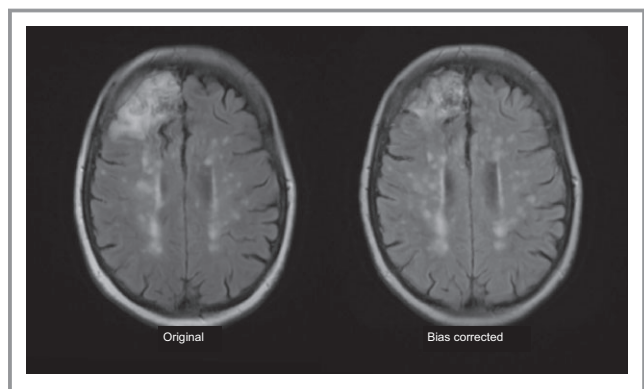
That WMH can reduce or disappear should not be a surprise if we accept that much of the signal change on FLAIR or T2 is due to shifts in water content and not just permanent myelin loss or axonal damage. WMH regression was noted in only one previous published case.<sup>164</sup> Most longitudinal studies report “no change” or “progression” of WMH. Three



**Figure 9.** Three different patients, but with similar amounts of WMH, scanned with slightly different slice thicknesses and at 1.5 or 3 T, illustrate the resulting differences in signal of WMH and normal tissues and hence the need for changes in tissue and WMH volume measurement methods. Slice thickness 1 mm<sup>2</sup> (A), 0.479 mm<sup>2</sup> (B), and 1 mm<sup>2</sup> (C) and MR scanner field strength—1.5 T (A and B) and 3 T (C) affect image appearance. Alterations in imaging parameters influence the image appearance and hence the performance of any software used to measure the WMH as all software ultimately rely on differences in signal characteristics between the tissue and lesions of interest. MR indicates magnetic resonance; WMH, white matter hyperintensities.

studies mentioned “minor regression” in some patients, but classified these as “no progression” without further exploration,<sup>165</sup> attributed reductions in WMH volume to measurement variability,<sup>166</sup> or reported (small) negative volume changes without comment.<sup>167</sup> We have noted reductions in WMH volume as well as increases, eg, about a third of 200

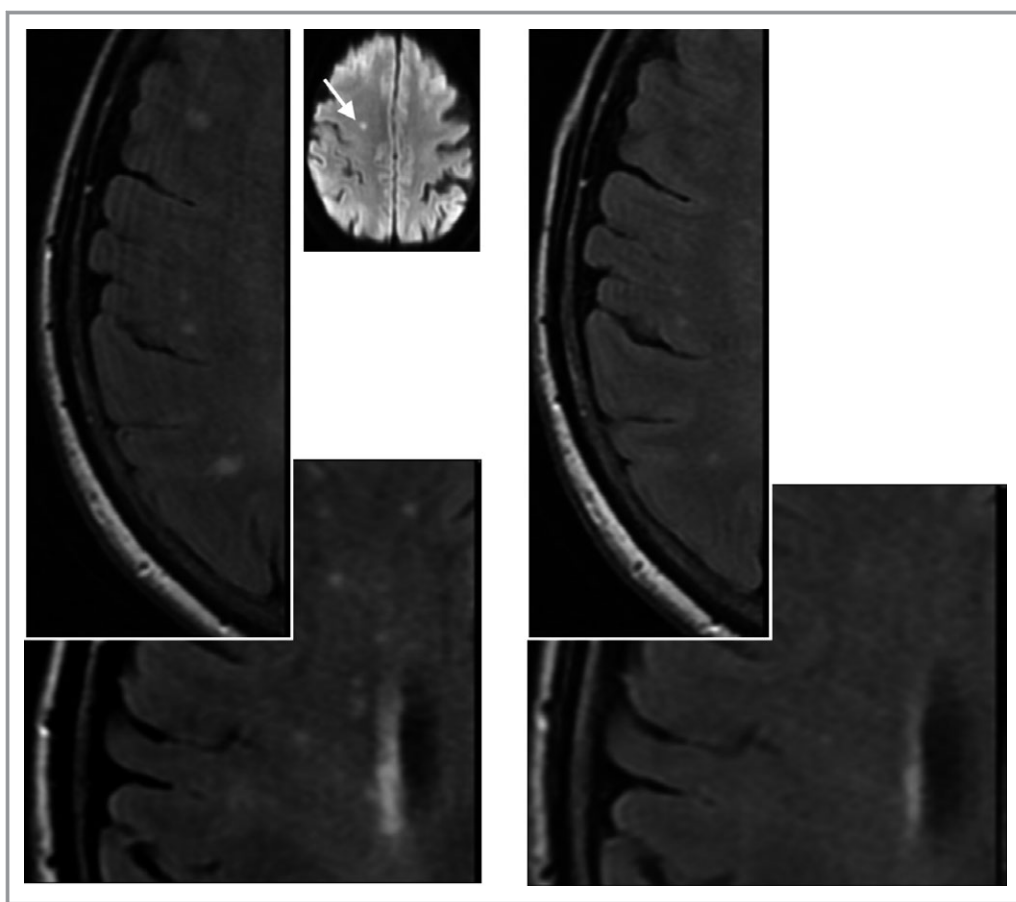
patients who presented with minor stroke had a small reduction in WMH volume on repeat MRI a year after stroke (in submission). In a few cases, the changes were more obvious (Figure 11). The reasons for reduction in WMH are unclear but might relate to improved vascular risk factor control. If some WMH are areas of tissue edema, then reduction in tissue edema would both reduce WMH and decrease brain volume. Indeed, in patients with CADASIL new WMH were associated with subtle increased brain volume.<sup>168</sup> Finally, fluctuations in WMH and white matter subvisible damage might account for the return to normal cognition seen in a few studies in patients with mild cognitive impairment.<sup>2</sup> Although these fluctuations have been attributed to recovery from depression, delirium, heart failure, or autoimmune disorders, the improving cognition could equally be attributed to resolution of transient fluid-related white matter damage before permanent axonal injury or demyelination has occurred.



**Figure 10.** Effect of incautious use of bias field correction on cortical infarct and WMH. The left image shows the original MR FLAIR image with a right frontal cortical infarct (arrow) and numerous WMH. Following bias field correction (left) the frontal infarct appears much smaller, some of the WMH have become more (eg, posterior areas) and some now appear split into smaller components (mid centrum semiovale) as the bias field smoothing software tries to “even out” the distribution of signal intensities across the image. FLAIR indicates fluid attenuation inversion recovery; MR, magnetic resonance; WMH, white matter hyperintensities.

## Implications for Clinical Practice

There is strong evidence that WMH are clinically important markers of increased risk of stroke, dementia, death, depression, impaired gait, and mobility, in cross-sectional and in longitudinal studies. They associate with brain damage such as global atrophy<sup>59</sup> and other features of small vessel brain damage,<sup>32</sup> with focal progressive visible brain damage,<sup>55,57</sup> are markers of underlying subvisible diffuse brain



**Figure 11.** Example of disappearing white matter hyperintensities. Left, scan at presentation with small subcortical infarct. Right, scan 1 year later. Inset image is diffusion image from original presentation showing small subcortical infarct that precipitated medical consultation. The images were obtained on the same scanner, using the same sequence with careful quality assurance maintained throughout. Note the lesions have become smaller and less white at 1 year compared with presentation.

damage,<sup>19,98,109,119</sup> and predict infarct growth and worse outcome after large artery stroke.<sup>60,61</sup> They could be considered as the neuroimaging marker of “brain frailty.”<sup>169</sup>

However, they should not be viewed only as “untreatable” or “permanent”: in vivo imaging indicates that water shifts and water content are prominent and represent early changes in WMH. Given the associations of WMH with traditional vascular risk factors, it is reasonable to manage risk factors according to current guidelines until further data from randomized controlled trials are available. Future trials should assess the effect of risk factor reduction by age group because common vascular risk factors may act differently at different ages. For example, blood pressure reduction in older people may need to work to less stringent target levels than in younger people because some older people with less reactive vasculature may become more dependent on blood pressure for cerebral perfusion than in subjects whose vasculature retains its elasticity and responsiveness. Similarly, cholesterol reduction may be relatively more important in older people to protect the brain than in younger people

where its main action may be on the heart. These speculations are based on emerging observations (eg, and the PODCAST trial, paper in preparation) and require careful testing in future trials.

Given the lack of readily available computational analysis methods, and the simplicity and durability of deriving visual WMH scores,<sup>170</sup> it is reasonable to use visual scores in clinical practice – at least these would provide some more precise quantification than purely descriptive reports. The addition of imaging methods such as DTI to routine clinical assessment of patients with minor stroke, cognitive, or aging would facilitate quantification of mean diffusivity or fractional anisotropy in normal-appearing white matter to indicate subvisible brain damage.

## Implications for Research

Research should target the enormous unfinished agenda that constitutes brain damage represented by WMH and diffuse small vessel disease. There should be more imaging-

neuropathology analyses of individual lesions in humans and in relevant experimental models. There should be more awareness that WMH are heterogeneous, can diminish as well as increase, that they represent a tip of the iceberg in terms of damage to the brain and lead to progressive global brain damage through local and remote brain tissue damage. More longitudinal multimodal imaging studies in well characterized subjects from middle to old age, from different ethnic, socioeconomic, and clinical backgrounds, are required to fully understand what influences the varying patterns of WMH and their associations with cognition, gait, mood, and vulnerability to stroke. Multimodal imaging is needed to assess parameters like MD, FA, MTR, T1, perfusion, etc, contemporaneously in normal and abnormal white and gray matter. Better methods to measure WMH are needed that are reliable and efficient, with minimal human input, for large population studies. These need to be more sophisticated to detect subtleties of WMH, change over time and response to treatment. These should be able to detect differences in intensity of WMH, not just size, and to recognize underlying general changes in brain white matter with increasing age and by exposure to risk factors. Better measurement methods are essential for new trials to test risk factor modification, repurposed drugs, new drugs, lifestyle modifications, etc, to prevent progressive brain damage from WMH. Finally, rather than focusing clinical trials on “Alzheimer’s disease” or “Vascular cognitive impairment”, clinical diagnoses which likely represent mixtures of pathologies, perhaps it would be better to focus on intermediary markers of brain damage, such as WMH, which likely reflect more specific pathologic mechanisms.

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## Disclosures

None.

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